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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/931,285	STUELPNAGEL ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on April 19, 2004 has been entered. The claims pending in this application are claims 1 and 3-23. Rejection and/ or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on April 19, 2004.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. For example, see page 1, third paragraph. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Note that applicant does not address this issue.

Specification

3. The disclosure is objected to because of the following informality: some reference recited in the specification is incomplete. For example, in page 16, lines 3-5, the specification recites "[A]n extensive guide to the hybridization of nucleic acids is found in Tijssen, Techniques in Biochemistry and Molecular Biology-Hybridization with Nucleic Acid Probes, 'overview of principles of hybridization and the strategy of nucleic acid assays'(1993).". However, applicant does not provide volume and page numbers for this reference.

Appropriate correction is required.

Note that applicant does not address this issue and the examiner has removed part of this objection after reviewing applicant's amendment in the specification filed on April 19, 2004.

Claim Objections

4. Claims 1, 12, 13, and 16 are objected to because of the following informalities: no period should appear after the label of each step, e.g., "a." should be --a)--.

Appropriate correction is required.

Response to Arguments

In page 9, third paragraph of applicant's remarks, applicant argues that "[A]pplicant has amended these claims according to the Examiner's suggestions. Accordingly, Applicant respectfully requests withdrawal of these objections".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because applicant's amendments on claims 1, 12, 13, and 16 do not overcome this objection.

5. Claim 12 is objected to because of the following informality: in view of steps d) and g), "a ligation enzyme" in step d) should be "a first ligation enzyme", "said ligation enzyme" in step d) should be "said first ligation enzyme", "a ligation enzyme" in step g) should be "a second ligation enzyme" and "said ligation enzyme" in step g) should be "said second ligation enzyme".

6. Claim 13 is objected to because of the following informality: "amplification enzyme" should be "an amplification enzyme".

7. Claim 16 is objected to because of the following informality: (1) " target nucleic acid" in preamble should be "a target nucleic acid"; (2) there are two "said first analysis comprising" and two "whereby said target nucleic acid is not consumed" in step b).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1 and 3-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 1 and 16 recite the limitation "wherein a signal obtained from said second analysis is not diminished more than 40% compared to a signal obtained from said first analysis" in the claims. There is insufficient antecedent basis for this limitation in the claims because the claims do not describe that a first analysis generates a signal and a second analysis generates a signal. Please clarify.

11. Claim 12 recites the limitation "wherein a signal obtained from said second ligation products is not diminished more than 40% compared to a signal obtained from said ligation products " in the claim. There is insufficient antecedent basis for this limitation in the claim because the claim does not describe that a signal is generated by said first ligation products and a signal is generated by said second ligation products. Furthermore, "said ligation products" in last line of claim 12 should be "said first ligation products". Please clarify.

12. Claim 12 is rejected as vague and indefinite in view of the phrase "said target nucleic

acid flanking a first target sequence" in step b), the phrase "said target nucleic acid flanking a second target sequence" in step f), and steps d) and g) since it is unclear whether a first target sequence or a second target sequence is part of said target nucleic acid or not. According to the meaning of "flanking", it appears that a first target sequence or a second target sequence is on the side of said target nucleic acid and is different from said target nucleic acid. However, from the steps (d) and (g), it appears that said target nucleic acid comprises a first target sequence and a second target sequence because said first ligation primers are complementary to said first target sequences while said second ligation primers are complementary to said second target sequences. Therefore, said first ligation primers and said second ligation primers in steps b) and f) of claim 12 do not correspond to said first ligation primers and said second ligation primers in steps d) and g) of claim 12. Please clarify.

Response to Arguments

In page 9, fourth paragraph bridging to page 10, first paragraph of applicant's remarks, applicant argues that "[C]laim 12 recites that the ligation primers hybridize to a target nucleic acid. The primers bind to a sequence within the target nucleic acid that flanks a target sequence. Accordingly, by the language of the claim the target nucleic acid corresponds to a nucleic acid molecule and the ligation primers bind to a sequence within that nucleic acid molecule. In step (b) the first ligation primers hybridize to the target nucleic acid in a region that flanks the target sequence of that target nucleic acid. Similarly, in step (f) the second ligation primers hybridize to the target nucleic acid to a region that flanks a second target sequence of that target nucleic acid. Accordingly, claim 12 is sufficiently clear to distinctly claim the invention and can include one or more target sequences within a target nucleic acid".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. In steps b) and f) of claim 12, it appears that a first target sequence or a second target sequence is on the side of said target nucleic acid and is different from said target nucleic acid while, in steps d) and g) of claim 12, it appears that said target nucleic acid comprises a first target sequence and a second target sequence because said first ligation primers are complementary to said first target sequences and said second ligation primers are complementary to said second target sequences. Therefore, said first ligation primers and said second ligation primers in steps b) and f) of claim 12 do not correspond to said first ligation primers and said second ligation primers in steps d) and g) of claim 12.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 3, 8-11, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khanna *et al.,* (Oncogene, 18, 27-38, 1999) in view of Monforte *et al.,* (US Patent No. 5,830,655, published on November 3, 1998).

Khanna *et al.,* teach multiplex PCR/LDR for detection of K-ras mutations in primary colon tumors.

Regarding claim 1, since Khanna *et al.,* teach to perform LDRs in the presence of ligases, detecting primers and mixtures of PCR products including wild type of K-ras gene and mutant K-ras gene from cell lines or tumor sample (see page 36, right column, last paragraph), Khanna *et al.,* disclose providing a composition comprising first primers (ie., detecting primers) and target nucleic acid (ie., mutant K-ras gene) as recited in step a) of claim 1. Since Khanna *et al.,* teach to perform different LDRs using different ratio of matched to mismatched template (see page 29, page 36, right column, last paragraph and Figure 2), Khanna *et al.,* disclose performing a first analysis of said target nucleic acid (ie., LDR with ratio of matched to mismatched template of 1:20) wherein said first analysis comprises contacting said first primers with said target nucleic acid whereby at least one of said first primers (ie., detecting primers) hybridizes with said target nucleic acid (ie., mutant K-ras gene) and contacting said hybridized first primers with an enzyme (ie., the ligase) such that said hybridized first primers are modified forming first modified primers (ie., the product of LDR with ratio of matched to mismatched template of 1:20) as recited in step b) of claim 1 and disclose performing a second analysis of said target nucleic acid (ie., LDR with ratio of matched to mismatched template of 1:50) wherein said second analysis comprises contacting second primers (ie., detecting primers) with said target nucleic acid (ie., mutant K-ras gene) whereby at least one of said second primers hybridizes with

said target nucleic acid and contacting said hybridized second primers with an enzyme (ie., the ligase) such that said hybridized second primers are modified forming second modified primers (ie., the product of LDR with ratio of matched to mismatched template of 1:50) as recited in step c) of claim 1. Since Khanna *et al.*, teach to separate unhybridized primers from the ligation products by gel electrophoresis (see page 36, right column, last paragraph) and claim 1 does not require that ii) of steps b) and c) must be performed before iii) of steps b) and c), Khanna *et al.*, disclose removing unhybridized first primers and removing second primers as recited in step b) of claim 1. Furthermore, Khanna *et al.*, teach to analyze and quantify fluorescent ligation products (see page 36, right column, last paragraph) wherein a signal obtained from said second analysis (ie., band in lane 5, the product of LDR with ratio of matched to mismatched template of 1:50) is not diminished more than 40% compared to a signal obtained from said first analysis (ie., band in lane 4, the product of LDR with ratio of matched to mismatched template of 1:20) as recited in claim 1 (see Figure 2, top right). Since mixtures of PCR products including wild type of K-ras gene and mutant K-ras gene from cell lines or tumor sample taught by Khanna *et al.*, are used as templates for LDRs that are not consumed in the reaction, Khanna *et al.*, disclose that said target nucleic acid (ie., mutant K-ras gene) is not consumed as recited in claim 1.

Regarding claim 3, since Khanna *et al.*, teach to analyze and quantify fluorescent ligation products (see page 36, right column, last paragraph), Khanna *et al.*, disclose detecting said first and second modified primers (ie., the products of LDRs with ratio of matched to mismatched template of 1:20 and with ratio of matched to mismatched template of 1:50).

Regarding claims 8-10, since Khanna *et al.*, teach that mixtures of PCR products including wild type of K-ras gene and mutant K-ras gene from cell lines or tumor sample are

amplified from human genomic DNAs (see page 36, right column), Khanna *et al.*, disclose that target nucleic acid comprises genomic DNA as recited in claim 8 wherein said genomic DNA comprises at least one copy of the genomic DNA from an organism as recited in claim 9 and wherein said organism is human as recited in claim 10.

Regarding claim 11, since the specification does not define what kind of sequence is an adapter sequence, a sequence in a detecting primer taught by Khanna *et al.*, is considered as an adapter sequence. Therefore, Khanna *et al.*, disclose at least one of said first and second primers (ie., a detecting primer taught by Khanna *et al.*,) comprises an adapter sequence as recited in claim 11.

Khanna *et al.*, do not disclose that either said first primer or said target nucleic acid is immobilized to at least one solid support as recited in step a) of claim 1 and claims 19 and 20.

Monforte *et al.*, teach to immobilize either a primer or a nucleic acid template by attachment to a solid support before a primer extension assay. Immobilization is via a covalent or non-covalent linkage (see last paragraph of column 6 and claims 1-3 in column 63).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 1,19, and 20 wherein either said first primer or said target nucleic acid is immobilized to at least one solid support in view of the prior art of Khanna *et al.*, and Monforte *et al.*. One having ordinary skill in the art would have been motivated to do so because Monforte *et al.*, have successfully attached either a primer or a nucleic acid template to a solid support before amplification of the nucleic acid template and the immobilization of either the primer or the nucleic acid template to a solid support would enhance separation of hybridized complexes formed by the nucleic acid template

and the hybridized probe or primer from the unhybridized probes or primers during the process of performing the methods recited in claims 1, 9, and 20. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to attach either a primer or a nucleic acid template to a solid support in order to separate hybridized complexes formed by the nucleic acid template and the hybridized probes or primers from the unhybridized probes or primers.

15. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khanna *et al.*, (1999) in view of Monforte *et al.*, (1998) as applied to claims 1, 3, 8-11, 19, and 20 above, and further in view of Zhang *et al.*, (US Patent No. 5,876,924, published on March 2, 1999).

The teachings of Khanna *et al.*, and Monforte *et al.*, have been summarized previously, *supra.*

Khanna *et al.*, and Monforte *et al.*, do not disclose amplifying said first and second modified primers to form first and second amplicons as recited in claim 4 and detecting said first and second amplicons as recited in claim 5.

Zhang *et al.*, teach amplifying modified primers (ie., the ligation products) to form amplicons and detecting said amplicons wherein said amplicons is detected by visualizing ethidium bromide stained amplicons on a gel (see Figures 2, 5, and 13, columns 14, 15, 43, and 44).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have amplified said first and second modified primers to form first and second amplicons as recited in claim 4 and have detected said first and second

amplicons as recited in claim 5 in view of the prior art of Khanna *et al.*, Monforte *et al.*, and Zhang *et al.*. One having ordinary skill in the art would have been motivated to do so because Zhang *et al.*, have successfully amplified modified primers (ie., the ligation products) to form amplicons and have successfully detected said amplicons, and amplification of said first and second modified primers (ie., the ligation products) would increase amount of said first and second modified primers so that the target nucleic acid can be indirectly detected when an insufficient amount of the target nucleic acid (can not be directly detected) is present in the sample (see Zhang *et al.*, see column 4, first paragraph). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to amplify said first and second modified primers to form first and second amplicons and detect said first and second amplicons as recited in claims 4 and 5.

16. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khanna *et al.*, (1999) in view of Monforte *et al.*, (1998) and Zhang *et al.*, (1999) as applied to claims 1, 3-5, 8-11, 19, and 20 above, and further in view of Uematsu *et al.*, (US Patent No. 6,225,064 B1, filed on October 7, 1999).

The teachings of Khanna *et al.*, Monforte *et al.*, and Zhang *et al.*, have been summarized previously, *supra.*

Khanna *et al.*, Monforte *et al.*, and Zhang *et al.*, do not disclose that said first and second amplicons comprise labels as recited in claim 6 wherein said first and second amplicons are labeled during said amplification as recited in claim 7.

Uematsu *et al.*, teach to amplify different nucleic acids using different fluorescent-labeled primers (see column 2, lines 52-61) so that amplified different nucleic acids are labeled with different fluorescent dyes. Therefore, Uematsu *et al.*, disclose that said first and second amplicons comprise labels as recited in claim 6 wherein said first and second amplicons are labeled during said amplification as recited in claim 7.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 6 and 7 wherein said first and second amplicons comprise labels and said first and second amplicons are labeled during said amplification in view of the prior art of Khanna *et al.*, Monforte *et al.*, Zhang *et al.*, and Uematsu *et al.*. One having ordinary skill in the art would have been motivated to do so because Uematsu *et al..*, have successfully amplify different nucleic acids using different fluorescent labeled primers so that amplified different nucleic acids are labeled with different fluorescent dyes, and incorporation of said first and second amplicons with different fluorescent dyes using different fluorescent labeled primers would enhance direct detection of said first and second amplicons by gel electrophoresis (see Uematsu *et al.*, column 9, second paragraph) so that one having ordinary skill in the art avoids to use toxic ethidium bromide during the process for detecting said first and second amplicons on the gel. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform the method recited in claims 6 and 7 wherein said first and second amplicons comprise labels and said first and second amplicons are labeled during said amplification.

Conclusion

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. No claim is allowed.

18. The combination of Khanna *et al.*, with other references in the record can not used to reject claims 12-18 and 21-23 since Khanna *et al.*, do not teach steps f) and g) of claim 12, step c) of claim 16, and analysis of at least 10-100 different target nucleic acids in a single reaction recited in claims 21-23.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (571)872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
August 19, 2004

FRANK LU
PATENT EXAMINER